

Our Docket No.: 01-00003  
Inventors: Gunderson et al.  
Serial No.: 10/600,634  
Filing Date: June 20, 2003

**REMARKS**

By the present communication, new claims 81 and 82 have been added and claims 2 and 20 have been canceled without prejudice to pursuing the subject matter of these claims in one or more applications claiming priority to the above-captioned application. Claims 8, 16, 27, 35, 52, 55-63, 65 and 73-77 were previously canceled without prejudice to pursuing the subject matter of these claims in one or more applications claiming priority to the above-captioned application. Following entry of the amendments claims 1, 3-7, 9-15, 17-19, 21-26, 28-34, 36-51, 53, 54, 64, 66-72 and 78-82 will be pending and under examination.

Claims 1 and 18 have been amended to include the subject matter of claims 2 and 20, respectively. Claim 9 has been amended to correct antecedent basis. Claims 37 and 64 have been amended, support for which can be found in the specification, for example, at page 60, lines 6-8. New claims 81 and 82 have been added, support for which can be found in the specification, for example, at page 14, lines 14-27 and page 59, line 28, through page 60, line 12. Accordingly, the amendments and new claims do not raise any issues of new matter. Furthermore, Applicants respectfully submit that entry of the amendments after final is proper because the amendments cancel claims, place the claims into condition for allowance or in better form for consideration on appeal, and do not raise new issues for consideration in accordance with 37 C.F.R. 1.116 and MPEP 714.12 and 714.13. Therefore, entry of the amendments is respectfully requested.

Also by the present communication the specification has been amended to properly identify trademarks. The amendments to the specification are formal in nature and do not raise any issues of new matter.

**Claim Objections**

The Office Action requests that claim 9 be corrected to no longer depend from a canceled claim. Applicants would like to thank the Examiner for pointing out the error and has amended claim 9 to correctly identify the claim from which it depends.

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The Office Action objects to claim 36, under 37 CFR 1.75(c), for allegedly failing to further limit the subject matter of claim 18 from which it depends. The Office Action alleges that claim 36 simply reiterates the limitations already present in step (c) of claim 18. Applicants respectfully disagree. Claim 18 recites in step (c) “directly detecting typable loci of said probe-fragment hybrids” (emphasis added) whereas claim 36 recites “the method of claim 18, wherein step (c) comprises directly detecting said typable loci of said fragments that hybridize to said probes” (emphasis added). The probe-fragment hybrids recited in claim 18 include both a probe and fragment whereas claim 36 recites the fragment of the hybrid recited in claim 18. Therefore, claim 36 further limits claim 18. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

#### Rejections Under 35 U.S.C. § 102

Claims 1, 3-7, 9-12, 14, 15, 17-19, 22-26, 28-31, 33, 34, 36, 37, 39-48, 50 and 51 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Schubert et al., American J. Pathol. 160:73-79 (2002) as evidenced by several references cited therein.

Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claims 1 and 18 have been amended to include the subject matter of claims 2 and 20, respectively. Claims 3-7, 9-12, 14, 15, 17, 19, 22-26, 28-31, 33, 34 and 36 depend from amended claims 1 or 18 and therefore also now include the subject matter of claims 2 or 20. Because claims 2 and 20 are not rejected over Schubert et al. the amendment renders the rejection moot with regard to claims 1, 3-7, 9-12, 14, 15, 17-19, 22-26, 28-31, 33, 34, 36.

Claim 37 has been amended such that step (c) recites “modifying said immobilized probe-fragment hybrids, wherein said modifying comprises incorporation of one or more nucleotides or nucleotide analogs in the probes or fragments of said probe-fragment hybrids” The Office points to page 75, column 1 of Schubert et al. and to the Lindblad-Toh et al. (*Nat. Biotech.* 18:1001-1005 (2000)) reference cited therein as allegedly describing modifying probe-fragment hybrids by staining with streptavidin-phycocerythrin and biotinylated anti-streptavidin antibody. The staining method although carried out on immobilized probe-fragment hybrids,

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does not include incorporating one or more nucleotides or nucleotide analogs as claimed. Rather, the fragments already include a biotin group added during the previous PCR amplification step (see page 1003, column 2, last paragraph of Lindblad-Toh et al.). Absent a description of all steps of claim 37 including step (c) as amended, Schubert et al. fails to anticipate claim 37 or claims 39-48, 50 and 51 which depend from claim 37.

For the reasons set forth above, Schubert et al. fails to anticipate the invention as claimed. Accordingly reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claims 1-3, 6, 7, 9-12, 14, 15, 17-20, 22, 25, 26, 28-31, 33, 34, 36, 37, 39, 42-48, 50, 51, 64, 72, and 78-80 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Dean et al. (US 6,617,137).

Applicants respectfully traverse the rejection. Claim 1 and 18 as amended require, inter alia, contacting said amplified representative population of genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed, wherein said amplified representative population of genome fragments comprises sequences identical to at least 90% of the genome. In contrast, Dean et al. does not describe a method in which an amplified representative population of genome fragments that is contacted to an array of probes comprises sequences identical to at least 90% of the genome. In rejecting claim 2 (now canceled) which recited that the amplified representative population of genome fragments comprises sequences identical to at least 90% of the genome, the Office Action alleges that Dean et al. describes a method of generating a representative population of genome fragments having sequences identical to at least 90% of the genome at Figure 6 and column 40, lines 51-61. Applicants disagree. For convenience, column 40, lines 51-61 of Dean et al. is reproduced below:

The most useful results from whole genome amplification are obtained when the amplification provides complete coverage of genomic sequences and minimal amplification bias. It is also preferred that the amplification product perform similarly to unamplified genomic DNA during subsequent genetic analysis. Genome coverage after MDA with heat denaturation of the template was examined for 10 randomly distributed SNPs after amplifications of 100-, 10,000-,

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or 100,000-fold. The presence of all loci was confirmed in the amplified DNA with the exception of one locus (PDK2-2) in 100,000-fold amplified DNA (Table 1).

Emphasis added. Furthermore, Dean et al. describes Figure 6 as follows

The relative representation of eight loci is depicted in FIG. 6 for amplification reactions carried out by three different WGA procedures. The X-axis represents the fold amplification in the amplified DNA used as template for quantitative PCR; the Y-axis is the locus representation, expressed as a percent, relative to input genomic DNA, which is calculated as the yield of quantitative PCR product from 1  $\mu$ g amplified DNA divided by the yield from 1  $\mu$ g genomic DNA control. The results for eight loci are indicated as follows; CXCR5, open diamonds; connexin40, open triangles; MKP1, open squares; CCR6, open circles; acidic ribosomal protein, filled diamonds; CCR1, filled triangles; cJUN, filled squares; CCR7, filled circles. FIG. 6A depicts the percent representation for eight loci derived from MDA-amplified DNA. FIG. 6B depicts the percent representation for eight loci present in DNA amplified using DOP-PCR. FIG. 6C depicts the percent representation for eight loci present in PEP-amplified DNA.

See column 46, line 60, through column 47, line 10 of Dean et al., emphasis added. The description in Dean et al. relied upon by the Office and reproduced above describes analysis of only 10 or 8 single nucleotide polymorphism loci in the MDA product. Given that the human genome that was subject to amplification in the MDA methods is about 3,100,000,000 nucleotides in length (i.e. 3.1 gigabases), the 8 to 10 nucleotides evaluated do not constitute at least 90% of the genome. Although Dean et al. asserts that presence of all 10 of the 10 SNPs examined was confirmed this sampling of only 10 nucleotides among the 3,100,000,000 nucleotides present in the genome is not nearly large enough to draw a statistically accurate conclusion regarding the representation of the entire genome in the amplified sample. More importantly, whether or not the small sampling of Dean et al. is indicative of the amount of DNA that was *produced* by MDA, the claims require *contacting immobilized probes* with genome fragments comprising sequences identical to at least 90% of the genome. There is no description in Dean et al. of contacting a population of immobilized probes with an amplified representative population of genome fragments that comprises sequences identical to at least 90% of the genome. Rather, Dean et al. at best describes contacting the MDA product with probes for only 10 SNPs in a TAQMAN<sup>®</sup> quantitative PCR analysis. Furthermore, because the quantitative PCR

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methods are carried out in solution, Dean et al. does not describe the use of a population of *immobilized* probes as claimed. Thus, claims 1 and 18 are not anticipated by Dean et al. Furthermore, claims 2-3, 6, 7, 9-12, 14, 15, 17, 19, 20, 22, 25, 26, 28-31, 33, 34 and 36 depend from and include all the limitations of claim 1 or 18 and are, therefore, also not anticipated by Dean et al.

Claims 37 and 64 have been amended such that step (c) recites "modifying said immobilized probe-fragment hybrids, wherein said modifying comprises incorporation of one or more nucleotides or nucleotide analogs in the probes or fragments of said probe-fragment hybrids." The Office points to column 34, line 60, through column 35, line 10 of Dean et al. as allegedly describing modifying immobilized probe-fragment hybrids by contacting biotin-labeled immobilized nucleic acids with alkaline-phoshatase-streptavidin conjugate. The staining method although carried out on immobilized probe-fragment hybrids, does not include incorporating one or more nucleotides or nucleotide analogs in the probes or fragments of the immobilized probe-fragment hybrids as claimed. Rather, in the methods of Dean et al. the fragments already include a biotin group that had been added prior to the immobilization step. Absent a description of all steps of claims 37 and 64 including step (c) as amended, Dean et al. fails to anticipate claim 37 and 64, or claims 39, 42-48, 50, 51, 72 and 80 which depend from claims 37 and 64.

For the reasons set forth above, Dean et al. fails to anticipate the invention as claimed. Accordingly reconsideration and withdrawal of this ground of rejection is respectfully requested.

#### Rejections Under 35 U.S.C. § 103

Claims 13, 32 and 49 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over either Schubert et al., American J. Pathol. 160:73-79 (2002) as evidenced by several references cited therein or Dean et al. (US 6,617,137) in view of Maldonado-Rodriguez et al., Mol. Biotech. 11:1-12 (1999).

Applicants respectfully traverse the rejection of claims 13 and 32 over Schubert et al. in view of Maldonado-Rodriguez et al. Claims 1 and 18 have been amended to include the subject matter of claims 2 and 20, respectively. Claims 13 and 32 depend from amended claims 1 and

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18, respectively and therefore also now include the subject matter of claims 2 or 20. Because claims 2 and 20 are not rejected over Schubert et al. in view of Maldonado-Rodriguez et al. the amendment renders the rejection moot with regard to claims 13 and 32 over Schubert et al. in view of Maldonado-Rodriguez et al.

Applicants respectfully traverse the rejection of claim 49 over Schubert et al. in view of Maldonado-Rodriguez et al. Claim 49 depends from claim 37 and therefore requires, *inter alia*, “modifying said immobilized probe-fragment hybrids, wherein said modifying comprises incorporation of one or more nucleotides or nucleotide analogs in the probes or fragments of said probe-fragment hybrids.” Applicants maintain for the reasons set forth above in response to the anticipation rejection that Schubert et al., even as evidenced by several references cited therein, does not teach or suggest the claimed methods at least because Schubert et al. does not teach or suggest a step of modifying immobilized probe-fragment hybrids as claimed. Maldonado-Rodriguez et al. does not cure the deficiencies of Schubert et al. Therefore, the references taken alone or in combination do not teach or suggest all elements of the claimed method and claim 49 is not obvious over Schubert et al. in view of Maldonado-Rodriguez et al.

Applicants respectfully traverse the rejection of claims 13 and 32 over Dean et al. in view of Maldonado-Rodriguez et al. Claims 13 and 32 depend from claims 1 and 18, respectively, and thus require, *inter alia*, “contacting said amplified representative population of genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed, wherein said amplified representative population of genome fragments comprises sequences identical to at least 90% of the genome.” Applicants maintain for the reasons set forth above in response to the anticipation rejection that Dean et al. does not teach or suggest the claimed methods at least because Dean et al. does not teach or suggest a method in which an amplified representative population of genome fragments that is contacted to an array of probes comprises sequences identical to at least 90% of the genome. Maldonado-Rodriguez et al. does not cure the deficiencies of Dean et al. Therefore, the references taken alone or in combination do not teach or suggest all elements

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of the claimed method and claims 13 and 32 are not obvious over Dean et al. in view of Maldonado-Rodriguez et al.

Applicants respectfully traverse the rejection of claim 49 over Dean et al. in view of Maldonado-Rodriguez et al. Claim 49 depends from claim 37 and therefore requires, *inter alia*, “modifying said immobilized probe-fragment hybrids, wherein said modifying comprises incorporation of one or more nucleotides or nucleotide analogs in the probes or fragments of said probe-fragment hybrids.” Applicants maintain for the reasons set forth above in response to the anticipation rejection that Dean et al. does not teach or suggest the claimed methods at least because Dean et al. does not teach or suggest modifying immobilized probe-fragment hybrids as claimed. Maldonado-Rodriguez et al. does not cure the deficiencies of Dean et al. Therefore, the references taken alone or in combination do not teach or suggest all elements of the claimed method and claim 49 is not obvious over Dean et al. in view of Maldonado-Rodriguez et al.

For the reasons set forth above, reconsideration and withdrawal of the rejection of claims 13, 32 and 49 over either Schubert et al., as evidenced by several references cited therein, or Dean et al. in view of Maldonado-Rodriguez et al. is respectfully requested.

Claims 21 and 38 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Dean et al. (US 6,617,137) in view of Lipshutz et al., Nature Genetics 21:20-24 (1999).

Applicants respectfully traverse the rejection of claim 21 over Dean et al. in view of Lipshutz et al. Claim 21 depends from claim 18 and thus requires, *inter alia*, “contacting said amplified representative population of genome fragments with a plurality of nucleic acid probes having sequences corresponding to said typable loci under conditions wherein probe-fragment hybrids are formed, wherein said amplified representative population of genome fragments comprises sequences identical to at least 90% of the genome.” Applicants maintain for the reasons set forth above in response to the anticipation rejection that Dean et al. does not teach or suggest the claimed methods at least because Dean et al. does not teach or suggest a method in which an amplified representative population of genome fragments that is contacted to an array of probes comprises sequences identical to at least 90% of the genome. Lipshutz et al. does not

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cure the deficiencies of Dean et al. because, whether or not Lipshutz et al. describes arrays having 7,000 to 40,000 probes, there is no teaching or suggestion of contacting the array with an amplified representative population of genome fragments comprising sequences identical to at least 90% of the genome. More specifically, Lipshutz et al., being directed to gene expression, describes contacting an array with a population of cDNAs or RNAs. Because far less than 90% of the sequence in the genome encodes for expressed products, Lipshutz et al. does not teach or suggest contacting immobilized probes with genome fragments comprising sequences identical to at least 90% of the genome. Therefore, the references taken alone or in combination do not teach or suggest all elements of the claimed method and claims 13 and 32 are not obvious over Dean et al. in view of Lipshutz et al.

Applicants respectfully traverse the rejection of claim 38 over Dean et al. in view of Lipshutz et al. Claim 38 depends from claim 37 and therefore requires, *inter alia*, "modifying said immobilized probe-fragment hybrids, wherein said modifying comprises incorporation of one or more nucleotides or nucleotide analogs in the probes or fragments of said probe-fragment hybrids." Applicants maintain for the reasons set forth above in response to the anticipation rejection that Dean et al. does not teach or suggest the claimed methods at least because Dean et al. does not teach or suggest modifying immobilized probe-fragment hybrids as claimed. Lipshutz et al. does not cure the deficiencies of Dean et al. Therefore, the references taken alone or in combination do not teach or suggest all elements of the claimed method and claim 38 is not obvious over Dean et al. in view of Lipshutz et al.

For the reasons set forth above, reconsideration and withdrawal of the rejection of claims 21 and 38 as allegedly obvious over Dean et al. in view of Lipshutz et al. is respectfully requested.

Claims 53 and 54 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over either Schubert et al., American J. Pathol. 160:73-79 (2002) as evidenced by several references cited therein or Dean et al. (US 6,617,137) in view of Pastinen et al., Genome Res. 7:606-614 (1997). In making the rejection, the Office alleges that Schubert et al. or Dean et al. describe claim 37 for the reasons set forth in the novelty rejections. The Office points out that Schubert et al. or Dean

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et al. describe genotyping based on array hybridization rather than solid-phase primer extension. The Office alleges that Pastinen et al. (1997) describes the use of a primer extension assay and that Pastinen et al. (1997) provides the motivation for modifying the method of Schubert et al. or Dean et al. to include a solid-phase primer extension assay because Pastinen et al. (1997) describes primer extension as having increased power of discrimination compared to hybridization methods.

Applicants respectfully traverse the rejection. Applicants disagree with the assertion in the Office Action that motivation to modify the methods of Schubert et al. or Dean et al. would have been provided by the description of increased discrimination for primer extension over hybridization in the abstract of Pastinen et al. (1997). The assertions in the abstract of Pastinen et al. (1997) must be taken in the context of the entire reference. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. See MPEP 2141.02 (VI) citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Furthermore, as stated at MPEP 706.02 (II), citation of and reliance upon an abstract without citation of and reliance upon the underlying scientific document is generally inappropriate where both the abstract and the underlying document are prior art. See *Ex parte Jones*, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001) (unpublished).

Although the abstract of Pastinen et al. states that “single-nucleotide primer extension is a promising principle for future high-throughput mutation detection and genotyping using high density DNA-chip technology,” the methods described in the body of the Pastinen et al. (1997) reference actually describe amplification of only 9 genomic fragments (see page 607, first column, last paragraph and page 607, second column, last paragraph). Any comparison of hybridization methods to primer extension methods by Pastinen et al. that supports the assertion in the abstract that primer extension provides a promising principle for the future is based on experiments carried out by contacting solid-phase probes with only these 9 fragments. In contrast, claims 53 and 54 require contacting a high complexity amplified representative population of genome fragments with a plurality of immobilized nucleic acid probes. The Office

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has not established that, even if one skilled in the art would have been motivated by the abstract of Pastinen et al. (1997) to try to modify the methods of Schubert et al. or Dean et al. to include primer extension, that one skilled in the art would also have had a reasonable expectation of success in making the modification given that the complexity of the genome fragments resulting from the methods of Schubert et al. or Dean et al. was orders of magnitude higher than the 9 fragments used in the primer extension methods of Pastinen et al. (1997).

Pastinen et al. (1997) casts plenty of doubt as to the success of the primer extension methods when used for a fragment mixture having complexity on the order required by the claims. For example, Pastinen et al. (1997) on page 609 in the section entitled "FUTURE PROSPECTS" states that

Already in its present form, the minisequencing primer array can be used as a specific and cost-effective alternative in the screening of relevant mutations in the Finnish population, where typically only one or a few mutations account for the vast majority of the disease alleles. However, to develop high throughput DNA chips for solid-phase minisequencing assays, some technical issues are to be addressed.

See page 609, column 2, last paragraph, emphasis added. Pastinen et al. (1997) goes on to describe one of the technical issues required to improve throughput beyond a "few mutations" as being sample preparation. Specifically, Pastinen et al. (1997) states

Despite the proceeding technical development related to miniaturized arrays for genotyping, a great challenge for the assays still lies in the sample preparation. At present, amplification of DNA templates by PCR limits the number of genomic fragments that can be analyzed efficiently. Methods are required by which a significantly larger number of fragments can be amplified or in which an amplification step is avoided. When the ubiquitous problem of sample preparation has been solved, minisequencing might be the reaction principle of choice for the implementation of high-throughput genotyping on miniaturized arrays in practice.

See page 610, column 1, through column 2, emphasis added. In view of the description in Pastinen et al. (1997) that they were only able to demonstrate the primer extension methods for a

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sample having a complexity of 9 fragments and that sample preparation was a great challenge for scaling up the methods, those skilled in the art would not have had a reasonable expectation of success in modifying the methods of Schubert et al. or Dean et al. to arrive at a method in which the amplified representative population of genome fragments that is contacted with immobilized probes and subjected to a primer extension assay was a high complexity representation, as claimed.

Furthermore, by the year 2000, the authors of Pastinen et al. (1997) had still not resolved the great challenge of scaling up to a level that even approached the use of a high complexity representation in a solid-phase primer extension assay as claimed. This is evident from, Pastinen et al. Genome Res. 10:1031-1042 (2000), which asserts that

There are two major hurdles for highly parallel screening of SNPs on microarrays. The first is the necessity of amplifying the DNA regions spanning the mutations or SNPs by the PCR to achieve sufficient sensitivity and specificity of detecting single-base variation in the complexity of the human genome limits the capacity of genotyping assays

See page 1032, col. 1, lines 4-10, emphasis added. Thus, Pastinen et al. (2000) questions whether microarrays can be used to detect SNPs with sufficient specificity in high complexity representations. Furthermore, as evidenced by the 2000 publication, the authors were still using amplicon mixtures having only low complexity three years after the Pastinen et al. (1997) publication cited by the Office. Specifically, the multiplex PCR methods employed by Pastinen et al. (2000) were carried out at a mere 7-8 plex level (see "Multiplex PCR Amplification" section on page 1038 of Pastinen et al. (2000)). The highest complexity mixture analyzed on an array by Pastinen et al. was a 106-plex mixture produced by spiking 99 non-target PCR products into a mixture of 7 target amplicons (see "Preparation of Templates for Complexity Testing" section on page 1039).

Even at the relatively low 106-plex level, Pastinen et al. (2000) reported difficulties that are indicative that those skilled in the art would not have had a reasonable expectation of success in scaling up to the level of a high complexity representation using the methods set forth in

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Pastinen et al. (1997). Specifically, Pastinen et al. (2000) observes that "decreased signal intensity is evident with increased template complexity" (page 1036, column 2, lines 10-11). In addition to reducing signal intensity, the presence of the 99 spiked PCR products also affected specificity. More specifically a mixture containing the 99 spiked PCR products, but none of the 7 targets, was included as a control for template-independent extension or cross reaction with non-specific target in Figure 5 (see the sample labeled 99\* in Figure 5 of Pastinen et al. (2000)). The results of Figure 5 show that the 99 non-target sequences produced non-specific signal intensity on the primer array even when the 7 targets for the primers on the array were absent. A further non-specific effect of the 99 non-target sequences on the primer arrays was that, even in the absence of the 7 target sequences, a ratio indicative of "correct" primer extension over misincorporation was detected. Thus, those skilled in the art would not have been motivated with a reasonable expectation of success to modify the methods of Schubert et al. or Dean et al. with the primer extension assay of Pastinen et al. (1997) to arrive at the claimed methods. Accordingly, claims 53 and 54 would not have been obvious and reconsideration and withdrawal of the rejection is respectfully requested.

Claims 64 and 66-72 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pastinen et al. Genome Res. 10:1031-1042 (2000) in view of Zhang et al. Proc. Natl. Acad. Sci. USA 89:5847-5851 (1992) and further in view of Grothues et al., Nucl. Acids Res. 21:1321-1322 (1993). In making the rejection the Office Action alleges that Pastinen et al. (2000) describes all of the elements of the claims but does not teach the use of random primers comprising a constant region in the in vitro transcription reaction nor do Pastinen et al. (2000) teach replication of the hybridized RNA fragments using locus specific primers. The Office Action alleges that Zhang et al. teaches a method of primer extension preamplification using random primers and that Grothues et al. teaches a method of amplification using tagged random primers. In regard to claims 64 and 67, the Office Action alleges that one skilled in the art would have been motivated to use the random primers of Zhang et al. in the genomic amplification method of Pastinen et al. (2000) in order to eliminate the need for optimization of a complicated multiplex PCR. In regard to claims 68-70, the Office alleges that the ordinary user of the method of Pastinen et al. (2000) would have been motivated to incorporate constant regions into the random and locus

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specific primers, thereby enabling an additional amplification reaction using primers complementary to the constant regions, thus providing another level of control over the accuracy of the hybridization results.

Applicants respectfully traverse the rejection. Applicants maintain, for the reasons made of record in the previous response that those skilled in the art would not have been motivated to modify the methods of Pastinen et al. (2000) to replace the single step multiplex-PCR methods with the random primer amplification methods of Grothues et al. or Zhang et al. because such a modification would replace the single-step method of Pastinen et al. (2000) with a multi-step process including separate amplification, purification and array analysis steps, whereas Pastinen et al. (2000) teaches that the very advantage of their methods is avoiding such a multiplicity of steps.

In the "response to arguments" section the Office Action appears to acknowledge that modification of the Pastinen et al. (2000) methods would result in decreased efficiency but holds that "one of ordinary skill would have recognized that results obtained quickly and inaccurately were of less value than results obtained slightly more slowly, but more accurately." Applicants can see no basis in the art of record for the conclusion that replacing the modification method of Pastinen et al. (2000) with the amplification methods of Grothues et al. or Zhang et al. would be "more accurate." Pastinen et al. (2000) uses a multiplex PCR approach for amplification. Zhang et al. does not provide any comparison of their PEP method with multiplex PCR, much less a comparison between the accuracy of the two methods. Zhang et al. does describe single-plex PCR as being limiting for single cell genetic analysis because the cell can be analyzed only once and suggests that PEP can be used to provide a DNA aliquot that is useful for multiple analyses (see the background of Zhang et al.). However, this is first of all a comparison to single-plex PCR, not the multiplex PCR method of Pastinen et al. (2000) and, secondly, this in no way addresses accuracy of the amplification methods as they pertain to amplifying a mixture of DNA fragments for use in the methods of Pastinen et al. (2000). Grothues et al. also does not provide any comparison of their T-PCR method with multiplex PCR, much less a comparison between the accuracy of the two methods. The only comparison between methods made by Grothues et

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al. is comparison to linker adapter PCR and random primer PCR (see page 1322, paragraph spanning first and second column of Grothues et al.). First, these methods are different from the multiplex PCR methods used by Pastinen et al. (2000) and, second, the comparison does not address accuracy of the different methods as they pertain to amplifying a mixture of DNA fragments for use in the methods of Pastinen et al. (2000). Absent any basis for the conclusion in the Office Action that the amplification methods of Grothues et al. or Zhang et al. are "more accurate" than the methods of Pastinen et al. (2000), Applicants maintain that the Office has not established a *prima facie* case of obviousness because it has not shown that there would have been motivation to modify the methods of Pastinen et al. (2000) to replace the single step multiplex-PCR methods with a multi-step process that Pastinen et al. (2000) suggests to avoid.

Furthermore, the Office has not established that, even if one skilled in the art would have been motivated to modify the methods of Pastinen et al. (2000) to replace the multiplex PCR methods with the amplification methods of Grothues et al. or Zhang et al. that one skilled in the art would also have had a reasonable expectation of success in making the modification. Claims 64 and 66-72 require, *inter alia*, hybridizing a high complexity representation of RNA fragments with a plurality of immobilized nucleic acid probes. As set forth above in regard to the obviousness rejection of claims 53 and 54, even at the relatively low 106-plex level, Pastinen et al. (2000) reported difficulties in decreased signal intensity and poor specificity for the primer extension-based detection method. Given that Grothues et al. and Zhang et al. describe their methods as producing far more complex mixtures of DNA fragments than those that Pastinen et al. (2000) grappled with, those skilled in the art would not have had a reasonable expectation that replacing the amplification methods of Pastinen et al. (2000) with those of Grothues et al. or Zhang et al. would result in successful detection using the primer extension-based methods of Pastinen et al. (2000). Absent motivation with a reasonable expectation of success to modify the methods of Pastinen et al. (2000) as proposed by the Office, the claims can not be obvious. Accordingly, reconsideration and withdrawal of the rejection of claims 64 and 66-72 is respectfully requested.

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**Double Patenting**

Claims 1, 3, 6, 9, 12, 18, 22, 25, 28, 31, 37, 39, 42, 44, 45, 48, 53, 54 and 78-80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 108, 119-121, 123 and 125-127 of co-pending Application 11/006,096.

Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claims 1 and 18 have been amended to include the subject matter of claims 2 and 20, respectively. Claims 3, 6, 9, 12, 22, 25, 28, 31, 78 and 79 depend from amended claims 1 or 18 and therefore also now include the subject matter of claims 2 or 20. Because claims 2 and 20 are not rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 108, 119-121, 123 and 125-127 of co-pending Application 11/006,096, the amendment renders the rejection moot with regard to claims 1, 3, 6, 9, 12, 18, 22, 25, 28, 31, 78 and 79.

With regard to claims 37, 39, 42, 44, 45, 48, 53, 54 and 80, Applicants will consider amending and/or canceling claims in one or both of the applications or filing a terminal disclaimer if necessary and appropriate when there is an indication of otherwise allowable subject matter.

Claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, 31, 37, 39, 40, 42, 44, 45, 48, 53 and 54 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78-80, 82, 85, 86, 90, 92, 93, 98, 104-106, 108, 110, 111, 115, 117, 118 and 123 of co-pending Application 10/872,141.

Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claims 1 and 18 have been amended to include the subject matter of claims 2 and 20, respectively. Claims 3, 4, 6, 9, 12, 22, 23, 25, 28, and 31 depend from amended claims 1 or 18 and therefore also now include the subject matter of claims 2 or 20. Because claims 2 and 20 are not rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78-80, 82, 85, 86, 90, 92, 93, 98,

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104-106, 108, 110, 111, 115, 117, 118 and 123 of co-pending Application 10/872,141, the amendment renders the rejection moot with regard to claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, and 31.

With regard to claims 37, 39, 40, 42, 44, 45, 48, 53 and 54, Applicants will consider amending and/or canceling claims in one or both of the applications or filing a terminal disclaimer if necessary and appropriate when there is an indication of otherwise allowable subject matter.

Claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, 31, 37, 39, 40, 42, 44, 45, 48, 53 and 54 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78, 82-84, 86, 89, 90, 94, 95, 100 and 107 of co-pending Application 10/871,513.

Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claims 1 and 18 have been amended to include the subject matter of claims 2 and 20, respectively. Claims 3, 4, 6, 9, 12, 22, 23, 25, 28, and 31 depend from amended claims 1 or 18 and therefore also now include the subject matter of claims 2 or 20. Because claims 2 and 20 are not rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78, 82-84, 86, 89, 90, 94, 95, 100 and 107 of co-pending Application 10/871,513, the amendment renders the rejection moot with regard to claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, and 31.

With regard to claims 37, 39, 40, 42, 44, 45, 48, 53 and 54, Applicants will consider amending and/or canceling claims in one or both of the applications or filing a terminal disclaimer if necessary and appropriate when there is an indication of otherwise allowable subject matter.

Claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, 31, 37, 39, 40, 42, 44, 45, 48, 53 and 54 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78, 81, 82, 84, 87, 91, 93, 94 and 104 of co-pending Application 10/870,710.

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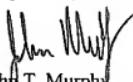
Applicants respectfully traverse the rejection. Nevertheless, in order to further prosecution of the application claims 1 and 18 have been amended to include the subject matter of claims 2 and 20, respectively. Claims 3, 4, 6, 9, 12, 22, 23, 25, 28, and 31 depend from amended claims 1 or 18 and therefore also now include the subject matter of claims 2 or 20. Because claims 2 and 20 are not rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 78, 81, 82, 84, 87, 91, 93, 94 and 104 of co-pending Application 10/870,710, the amendment renders the rejection moot with regard to claims 1, 3, 4, 6, 9, 12, 18, 22, 23, 25, 28, and 31.

With regard to claims 37, 39, 40, 42, 44, 45, 48, 53 and 54, Applicants will consider amending and/or canceling claims in one or both of the applications or filing a terminal disclaimer if necessary and appropriate when there is an indication of otherwise allowable subject matter.

#### CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent should there be any questions.

Respectfully submitted,

  
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